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Total joint replacement in inhibitor-positive haemophilia : Long-term outcome analysis in fifteen patients

Danielson, Heidi

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Retrospective Study

Total joint replacement in inhibitor-positive haemophilia: Long-term outcome analysis in fifteen patients

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Abstract

AIM

To collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

METHODS

We report our 21-year, single-centre cumulative experience of 15 joint arthroplasties in six inhibitor patients.

RESULTS

Two low responder inhibitor patients were in the early days treated with FVIII, whereas bypassing agents were used in the rest of the high responder patients. The primary haemostatic outcome was good in 8/15, fair in 4/15 and poor in 3/15 operations. The overall patient outcome, including joint health and patient satisfaction, was good in 10/15, fair 4/15 and poor in 1/15. No deep infections were observed. Cost analysis was most beneficial in low responders and in two immune-tolerized, high responder patients. In all cases, factor replacement comprised the main treatment costs.

CONCLUSION

Our experience supports the initial use of bypassing agents as well as preoperative immune-tolerance induction when possible. Despite the challenges of haemostasis and severe joint disease, total joint arthroplasty can reach a good outcome, even in inhibitor patients. The risk for deep infection might be smaller than previously reported. Individual planning, intense multidisciplinary teamwork

and execution of operations should be centralised in a professional unit.

Key words: Haemophilia; Joint replacement; Inhibitor; Cost analysis; Arthroplasty

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Core tip: There are only few reports including joint arthroplasties on inhibitor-positive haemophilia patients. Generally the focus is mainly on immediate haemostatic outcome leaving the long-term orthopaedic results unreported. Our study brings out the importance of long-term and overall outcome when performing elective life-quality surgery. Management of inhibitor patients is especially challenging regarding not only the operative treatment but also the costs. As the health economic analysis of the topic is lacking, we provide new data. According to our cost analysis, preoperative immune-tolerance induction for high responder patients will bring cost- and outcome benefit both in surgery and preventing postoperative bleeds.

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INTRODUCTION

Total joint arthroplasty covered with coagulation factor replacement therapy is the treatment of choice in severe haemophilic arthropathy when conservative treatment has failed. The failure to stabilize the joint disease is usually due to the late initiation of secondary prophylaxis with replacement therapy. Patients may develop inhibitors to their factor replacement therapy due to the foreign protein and have thus often missed the prophylactic replacement therapy and surgical treatment because of the fear of bleeds and the high costs of the treatment. In the literature, the inhibitor prevalence is around 10% among the adult patient population, mainly affected by the earlier treatment and availability of immune-tolerance induction (ITI) therapy^[1-3].

The appropriate replacement therapy depends on the patient's individualized response, which is not always similar - nor predictable - at each haemostatic challenge or management strategy. The introduction of bypassing agents has enabled total joint replacements also for high responder inhibitor patients^[4]. However, the use of these products is costly.

The reports on joint arthroplasties in inhibitor patients are mainly case-based, and established standards of the management of these operations are scanty^[5-7]. At Orton Orthopaedic Hospital of Invalid Foundation, centralised

operative treatment of haemophilic joint disease has been carried out already since the 1970s. The haematological and laboratory support has been available by Red Cross Transfusion Central from 1957, and from 2002 also by the Helsinki University Hospital Coagulation Disorders unit. The first total hip replacement (THR) for a haemophilia patient in Finland was performed in 1982, and the first knee replacement (TKR) in 1984. The first TKR on a patient with recognized inhibitors was performed in 1991. We report our cumulative experience of 21 years of 15 joint arthroplasties in six haemophilia inhibitor patients.

MATERIALS AND METHODS

From 1991 to 2012, six haemophilia patients with inhibitors (two low; inhibitor titre < or equal to 5 BU/mL) and four high responders; inhibitor titre > 5 IU/mL) were operated on (Tables 1 and 2). The 15 surgical procedures consisted of seven primary TKRs (in two patients, bilateral), one unicondylar knee arthroplasty, one glenohumeral replacement, two ankle arthroplasties, one THR and three knee revision arthroplasties.

Two patients were low responders (inhibitor titre < 5 BU/mL). Four patients who had a history of high inhibitor titre (> 5 BU/mL) were classified as high responders, but the titre immediately prior to surgery was < 5 BU/mL. Two high-titre inhibitor patients underwent successful ITI as a part of the ObsITI protocol at a later stage (from 2010 onwards) of the follow-up. Five patients (83%) had a history of hepatitis C. One patient also was antibody-positive for hepatitis B. None of the patients was HIV positive.

To manage surgery during the early 1990s, the historical peak inhibitor titre, whether low or high (< or > 5 BU/mL), dictated the strategy. Traditionally, immediately preoperatively in the absence of FVIII inhibitory antibodies (*i.e.*, confirmed normal recovery and half-life of FVIII), either recombinant or plasma-derived FVIII is infused intravenously to secure haemostasis by reaching normal FVIII levels (usually 80%-100%). In contrast, the presence of inhibitors neutralise FVIII, and for the surgery FVIII bypassing agents, either activated prothrombin complex concentrate (aPCC, FeibaR) or recombinant activated Factor VII (rFVIIa, NovoSeven), are the current effective options to maintain surgical haemostasis of blood. The specific agent is chosen according to the individual bleeding phenotype, history and patient weight. Initially, either cryoprecipitate or a plasma-derived FVIII (pdFVIII) was used in all low responders and initially in high responders having a preoperative low inhibitor titre, with the objective to switch to a bypassing agent once the inhibitor titre inclined. Low responders (Patients A and B) were initially treated with their standard replacement therapy: Cryoprecipitate (AHF-20®, *n* = 1/8) or coagulation factor VIII (pdFVIII, Amofil®, *n* = 7/8). For the high responder patients (C-F), the treatment was either activated prothrombin complex concentrate (aPCC, FEIBA®) or

Table 1 Main surgical operations in patients (A and B) with the low historical inhibitor titre (< 5 BU/mL)

Patient and operations (model)	Haemophilia therapy	Primary haemostatic outcome	Surgical outcome
A			
TKR (cruciate retaining)	Cryo (AHF-20) → pdFVIII	Good	Good
TKR (cruciate retaining)	pdFVIII	Good	Good
Ankle arthroplasty	pdFVIII	Good	Good
Ankle arthroplasty	pdFVIII	Good	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Fair	Good
Knee revision arthroplasty (reconstructive)	rFVIII	Good	Good
B			
Knee hemiarthroplasty (unicondylar)	pdFVIII	Good	Poor
Revision arthroplasty (cruciate retaining)	pdFVIII → rFVIIa	Fair	Good

In A, six operations and in B, two operations were performed. TKR: Total knee replacement; pdFVIII: Plasma-derived factor VIII; rFVIII: Recombinant FVIII.

Table 2 Main surgical operations in the patients (C-F) with the high historical inhibitor titre

Patient and operations (model)	Replacement therapy	Primary haemostatic outcome	Surgical outcome ROM/pain
C			
TKR bilateral (hinge + posterior stabilised)	pdFVIII → aPCC	Poor	Fair
THR (uncemented)	rFVIII	Good	Good
D			
TKR bilateral (reconstructive)	aPCC → rFVIIa	Fair	Fair
E			
TKR (posterior stabilized)	aPCC → rFVIIa	Poor	Good
F			
Glenohumeral hemiarthroplasty	rFVIII	Good	Good

ROM: Range of motion; TKR: Total knee replacement; THR: Total hip replacement; aPCC: Activated prothrombinase complex concentrate.

recombinant activated factor VIIa (rFVIIa, NovoSeven®). In one case, the treatment was started with pdFVIII, but changed to aPCC when the inhibitor titre arose.

The routine blood coagulation tests were monitored daily during the FVIII replacement period to capture FVIII: C clotting activity or during bypassing therapy to capture the possible development of disseminated intravascular coagulation (DIC), anaemia or thrombocytopenia. Cefuroxime was used as standard antibiotic prophylaxis (or clindamycin, in case of allergy).

After TKR, continuous passive motion (CPM) treatment was started at the 2nd–7th postoperative day. After THR, immediate full body weight bearing was allowed, if the blood and haemostatic status supported the decision. After ankle arthroplasties, half-weight bearing with walker orthosis was recommended for 6–8 wk. After glenohumeral arthroplasty, the upper arm was immobilized in an arm sling for 4 wk and only passive mobilization for 6 wk was allowed.

Primary haemostatic outcome was considered good if the postoperative bleeding did not differ from the normal arthroplasty, fair if there were additional bleeds and poor if there were massive or repetitive additional bleeds that were difficult to manage.

The statistical analysis was carried out using the SPSS 20.0, Lead Technologies, Inc. statistical software system. For analysis, a paired-samples *T*-test was used. In this study, a *P*-value < 0.05 (two-sided probability)

was considered significant.

RESULTS

Low responders (A and B). Two low inhibitor titre patients underwent several operations, the details of which are captured in Table 1.

In Patient A, TKR was carried out under cryoprecipitate coverage. At three days, the treatment had to be changed to pdFVIII when the FVIII: C response started to decline. The haemostatic outcome was good.

Three years later, a second primary TKR with pdFVIII replacement therapy was performed. The inhibitor titre remained low, and the haemostatic and surgical outcomes were good. Two years later, the patient experienced recurrent knee bleeds at the recent TKR site. Three arthroscopical synovectomies were performed under pdFVIII replacement, while any vascular anomaly was excluded by popliteal angiography^[8,9]. After each synovectomy, the bleeding tendency decreased temporarily for a few months. Finally, the bleeds ceased with Holmium isotope radiosynoviorthesis. Additionally, two total ankle arthroplasties were performed successfully under pdFVIII coverage with good haemostatic and primary outcomes.

Later, the patient underwent revision knee arthroplasties due to aseptic loosening of the components. Both arthroplasties were performed using rFVIII. After

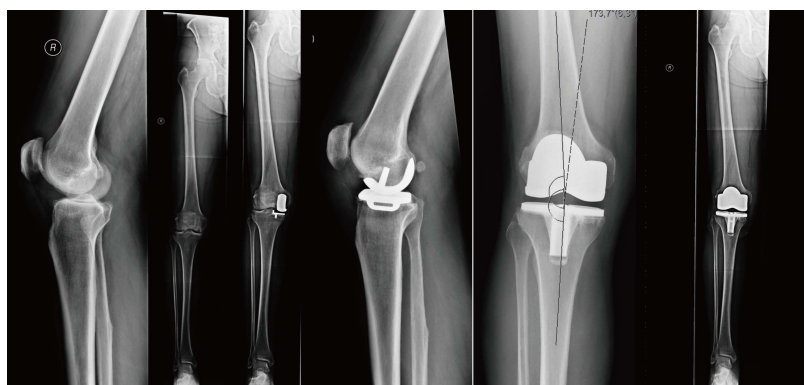


Figure 1 Unicondylar knee replacement and revision arthroplasty.

the first operation, the patient experienced a knee bleed at 8 d while on continuous replacement therapy, which was treated with higher dosing of rFVIII. There was a temporary rise in the FVIII antibody, but the final outcome was good. The second knee operation resulted in good haemostatic and overall outcome.

Patient B had experienced only occasional spontaneous bleeding episodes. Before the primary operation, he was devoid of inhibitor history. He suffered from posttraumatic medial knee arthrosis, and unicondylar knee replacement was performed with a good haemostatic outcome using pdFVIII. However, the patient needed revision arthroplasty 9 mo after the primary operation. Next, the replacement therapy was started with pdFVIII, and at 12 d postoperatively, the inhibitor titre raised the replacement therapy was switched to rFVIIa with good haemostatic outcome (Figure 1).

In conclusion, the two low responder inhibitor patients were managed successfully with FVIII concentrate, while the inhibitor titre remained low. Individually and according to the type of surgery, the FVIII was switched to bypassing agents when the inhibitor titre rose. One postoperative bleed in association with 8 operations occurred without long-term consequences.

High-responders, patients C-F

The surgical details of Patients C-F are presented in Table 2. In Patient C with bilateral primary knee arthroplasty, the preoperative inhibitor titre was < 5 BU/mL, and the operation was carried out without complications using pdFVIII. At five days when the inhibitor titre rose, however, the patient experienced bilateral knee bleeds and aPCC was started. The dose (up to 200–250 U/kg) had to be increased for several days due to a fair haemostatic response. DIC or deep venous thrombosis did not develop. After 5.5 years, the patient underwent a successful ITI therapy with rFVIII, and a primary THR could be performed with rFVIII 6 mo later with good haemostatic and surgical outcome. The recovery and half-life of rFVIII were appropriate, and the inhibitor did not reoccur throughout the early and later follow-up.

Patient D had bilateral TKR with aPCC as replacement therapy. At 8 d the patient experienced a severe knee

bleed, which ceased with rFVIIa [two doses of 5 mg (90 μ g/kg *iv*) at 2 h interval]. Next, aPCC was re-administered (at 200 IU/kg) but the patient bled with regard to the operated knee twice, at days 11 and 14. After the third bleed, the replacement therapy was carried out with rFVIIa for four days and thereafter with sequential aPCC and rFVIIa for two weeks.

Patient E underwent TKR with aPCC as replacement therapy pre- and perioperatively. At two days, he suddenly bled a lot (800 mL/30 min) with regard to his operated knee. A bolus of 12 mg of rFVIIa (220 μ g/kg) stopped the bleed immediately. The replacement therapy was continued with rFVIIa (6 mg every 2 h) for several days, and the haemostatic outcome was finally optimal.

Patient F had a history of high inhibitor titre and successful ITI with rFVIII one year preoperatively. He underwent glenohumeral hemiarthroplasty with good haemostatic outcome and without an increase of the inhibitor titre during the follow-up.

Overall, in 5 operations out of 12, the patients experienced major bleeds at 2–8 d postoperatively. Albeit this initial haemostatic response was either fair or even poor in two patients, the joint outcome was good. One patient had bilateral knee operation initially managed with pdFVIII, during which there was the reactivation of the inhibitor and both-sided bleeds occurred. He had the poor haemostatic response. However, the complication was controlled by switching the therapy to bypassing agents. A single bypassing therapy did not necessarily manage to control haemostasis, but the switch between aPCC and rFVIIa or their sequential use finally secured the haemostatic outcome.

Primary arthroplasties

The mean follow-up for patients with primary TKR (eight arthroplasties) was 7.3 years (0.3–20.3, SD 7.6). The median age of the patients at the time of the operation was 48.4 years (35.4–66.1, SD 10.9). The median hospital stay was 19.6 d (10–25, SD 6.1). The range of motion (ROM) improved from mean 81.9° flexion to 96.9° (SD 17.1 and 11.9, $P = 0.07$) and from mean 21.3° extension deficiency to 7.5° (SD 12.7 and 8.4, $P = 0.09$). One high

responder patient (Patient D) with severe knee flexion contracture with bilateral knee arthroplasty had a patellar fracture. It was observed at the two-month control and treated conservatively with orthosis. No deep infections were observed.

The two ankle arthroplasties were performed without complications to the same low responder Patient A. The patient had severe haemophilic arthropathy without significant deformation or bone loss in both ankles, and the preoperative walking distance had diminished below 500 m. Preoperative ROM in both ankles was from neutral position to 20° plantar flexion and primary outcome was from 5° dorsiflexion to 30° of plantar flexion, respectively. In 6.1 and 7.0 years follow-up 0°-20° ROM in plantar flexion of both ankles was observed. The patient could stand on his toes, walking ability was improved to 2 km and both ankles were pain-free. Radiologically, the components were in good position without signs of loosening or other complications.

The total hip arthroplasty for the high responder Patient C with a preoperative successful ITI was performed with an excellent haemostatic and primary outcome. At the 2-mo follow-up, the patient had a pain-free joint and ROM 0°-90° extension-flexion, 20° rotation and 40° abduction. The radiographic control showed a good position of the prosthesis.

The high responder Patient F with glenohumeral hemiarthroplasty had also undergone recent preoperative ITI. The patient had a painful haemophilic arthropathy with restricted ROM (abduction 45°, flexion 60° and outer rotation -10°), severe prolonged pain problems and an addiction to opiates. The surgery succeeded well under rFVIII coverage. The pain significantly diminished, and at the 7-mo follow-up, ROM substantially improved (abduction 80°/110° using scapulae, flexion 90°/130° using scapulae and outer rotation 45°) with pain-free peripheral movements. The X-rays showed a good position of the prosthesis.

Revision arthroplasties

Two revision knee arthroplasties using reconstructive prostheses for Patient A were performed at 17.7 and 15.7 years after primary operations because of loosening of the components. The hospital stay was 16 and 11 d, and CPM treatment was started three and five days after the operation, respectively. The postoperative mobility was 0°-100° and 0°-110° at 2.1 years and 1.8 years follow-up. After the first operation there was an initial bleed, but the joint outcome was good. The second operation and primary rehabilitation were successful with both good haemostatic and primary outcome. Five months postoperatively, a bacterial prepatellar bursitis was treated with peroral antibiotics. No deep infection was detected and the patient recovered well.

The third knee revision arthroplasty was performed at 9 mo after a primary operation for Patient B because of loosening of the components. The patient had suffered from posttraumatic medial knee arthrosis, and the

joint problem was considered primarily posttraumatic rather than haemophilic arthropathy. For these reasons, unicondylar knee replacement was performed. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. Neither bacteria nor the signs of infection were detected. In spite of the fair haemostatic outcome, the joint outcome was good with 0°-110° ROM and freedom from pain at the 3.5-year follow-up. Radiologically, the components were in good position, and the walking ability had improved from 100 m to over one kilometre.

Cost analysis

Since 2005 in Orton Orthopaedic Hospital, 11 major orthopaedic procedures (13 arthroplasties) on inhibitor patients were performed (Table 3). Among the high responder patients when aPCC and/or rFVIIa were needed, the total costs varied between 350900-500400 Euros. In these cases, the replacement therapy covered the great majority, *i.e.*, 87%-94%, of the total costs, even though two of the three operations were bilateral. Of the two low responders and in two cases among high responder patients after ITI, the replacement therapy costs were lower, being 59%-81% of the total costs. The total costs of these operations were also clearly lower compared to the high responders with an active inhibitor: About 1/5 - 1/3, *i.e.*, 47200-103200 Euros, in the low responders and about 1/10, *i.e.*, 43300-49800 Euros, in the two high responders having undergone ITI.

High responder patients with postoperative inhibitor formation had also a longer hospital stay (15-24 d) compared with the low responder patients (8-18 d) or the high responders with preoperative ITI (8-9 d). However, two of the three operations in high responder patients were also bilateral.

DISCUSSION

According to the guidelines of World Federation of Haemophilia^[10], joint replacement surgery for haemophilia patients requires multidisciplinary teamwork. Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported^[5-7,11-16]. However, there are only a few reports including joint arthroplasties on inhibitor patients^[7,11,12,16-19] with scant follow-up data. As this is a rare patient group, randomised controlled trials are not - and are not likely - to become available.

In our report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. Along prolonged rehabilitation, postoperative bleeding complications increase costs and reduce the patient's

Table 3 Cost analysis of arthroplasties on inhibitor patients since 2005

Resp	Operation		Component	TOT eur	HT ² eur	HT (%) ³	Product [®]	Hospital stay(d)
Low	Knee revision arthroplasty	Unilateral	Reconstructive	103200	75700	73	Kogenate Bayer	18
Low	Knee revision arthroplasty	Unilateral	Reconstructive	95400	66900	70	Kogenate Bayer	11
Low	Ankle arthroplasty	Unilateral	Primary ankle	47200	35600	75	Kogenate Bayer	10
Low	Ankle arthroplasty	Unilateral	Primary ankle	60200	48800	81	Kogenate Bayer	12
Low	Knee hemiarthroplasty	Unilateral	Unicondylar	51500	41600	81	Amofil	9
Low	Knee revision arthroplasty	Unilateral	Cruciate retaining	50200	36300	72	Amofil	8
High	Knee arthroplasty	Bilateral	Ps ⁴ + hinge	350900	305500	87	Amofil	24
							FEIBA	
High	Hip arthroplasty	Unilateral	Primary uncemented	43300	27800	64	ReFacto AF ¹	8
High	Knee arthroplasty	Bilateral	Reconstructive	500400	445100	89	FEIBA	24
							NovoSeven	
High	Knee arthroplasty	Unilateral	Ps ⁴	409900	386100	94	FEIBA	15
							NovoSeven	
High	Glenohumeral arthroplasty	Unilateral	Primary glenohumeral	49800	29300	59	ReFacto AF ¹	9

¹Successful preoperative ITI; ²HT haemophilia therapy (costs of replacement therapy); ³Procentual costs of replacement therapy; ⁴Ps posterior stabilized; Resp: Inhibitor responder (low = historical inhibitor titre < 5 BU/mL, high = historical inhibitor titre > 6 BU/mL).

quality of life by increasing pain and disability. Every effort should focus on the avoidance of postoperative bleeds. Point of care monitoring with thromboelastography or a calibrated automated thrombogram may help in treatment decisions as the therapy unexpectedly may fail^[20]. The therapy should be started preferentially with the bypassing agents, and the team should work intimately together with bedside visits to secure the haemostasis when the patient is to be mobilized. According to our experience, the use of cold to reduce swelling and pain may not be optimal, as cooling in the knee may impair the early haemostatic response. Finally, the tailored use of tranexamic acid, not only with rFVIIa but also with aPCC, may turn beneficial^[21-23].

Radiosynovectomy has been shown to be an effective treatment in chronic haemophilic synovitis, diminishing pain and bleeding occurrence^[24-26]. One of our patients had joint bleeds after TKR with only a temporary help from arthroscopical synovectomies. Even angiography was performed to exclude vascular anomalies, which have been reported in the form of pseudoaneurysms and their rupture after joint surgery or even natively^[8]. Radiosynoviorthesis with Holmium isotope finally ended the bleeding episodes. The case is similar to Papavasiliou's report^[27] of successful radiosynovectomy after TKR, although that patient was not reported to have inhibitors. In our experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

The risk of infection (early- and late-onset) is known to be greater in haemophilia patients undergoing arthroplasty compared with the non-haemophilia population^[21,28]. In our report there was one prepatellar bursitis, but deep infections were absent. However, the follow-up times were partly short.

In one case, a unicondylar knee replacement was performed to a patient devoid of previous inhibitor history. The patient suffered from posttraumatic medial arthrosis and the primary hemostatic outcome was good.

However, a rapid revision (9 mo postoperatively) was performed because of aseptic loosening of components. The loosening was thought to result from mechanical factors, but the compromised haemostasis by haemophilia may also play a role. In our experience, we do not recommend unicondylar arthroplasty to a patient with haemophilia.

Surgery for patients with inhibitors is expensive and highly demanding. In our report, in 3/8 primary TKRs, revision-type (constrained or reconstructive) prostheses were used because of severe bone defects and soft tissue degeneration. According to our cost analysis, the operation itself including the components, surveillance, medication and hospital stay was less significant, whereas the major cost comprised of the haemostatic replacement therapy. This was especially evident among the high responder patients and when bypassing agents were needed, thus constituting ca. 90% of total costs. Instead, in high responder cases that had undergone preoperative ITI, the cost of replacement therapy was similar to the low responder patients' cases and those of regular haemophilia management. The hospital stay was prolonged for the high responder patients, albeit two of the three operations were bilateral arthroplasties. In our opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds^[29-31]. The disadvantages of ITI are its partial success rates and time constraints, under conditions where there is an urgent need for surgery.

When determining the optimal timing for arthroplasty one must consider the grade of arthrosis, the patient's age, the supposed survival of the chosen prosthesis, as well as the risk of complications. Also, working ability, the status of other joints, osteoporosis and the estimated overall prognosis are to be taken into account. For optimal prognosis, the operation should be performed before permanent joint contractures. From the haematological point of view, the patient

characteristics, plan for replacement therapy for surgery and rehabilitation must be meticulously evaluated preoperatively. An appropriate rehabilitation program prior to and after surgery takes into account other joints and their functionality during recovery in order not to induce other joint problems. In the surgery of haemophilia patients, especially with inhibitors, the comprehensive medical team has to observe the patient for early haemostatic symptoms and signs. Therefore, it is essential that these operations are centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

COMMENTS

Background

Total joint arthroplasty covered with coagulation factor replacement is the treatment of choice in severe haemophilic arthropathy. Inhibitor patients are especially challenging regarding not only the operation and haemostasis management but also the costs since the treatment can be very expensive. The aim was to collect data from joint replacement in inhibitor patients, evaluate haemostatic and patient outcomes, and analyse the costs.

Research frontiers

Despite the demanding surgery, good results among haemophilia patients with inhibitors have been previously reported. However, there are only a few reports including joint arthroplasties on inhibitor patients with scant follow-up data.

Innovations and breakthroughs

In this report, the primary haemostatic outcome was good in half of the patients and poor in 20% of the high responder patients, and improved only with switching between the bypassing agents. However, the primary surgical outcome turned out fairly well, even in those patients who initially had a poor haemostatic outcome. In the authors' opinion, preoperative immune-tolerance induction (ITI) for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty.

Applications

In the authors' opinion, preoperative ITI for high responder patients will bring cost and outcome benefits, both in surgery and the prevention of postoperative bleeds. Also, in the authors' experience, radiosynoviorthesis seems to be effective also for patients who have undergone joint arthroplasty. Surgery of haemophilia patients should be centralized in a professional unit with the availability of skilled surgeons and haematologists having access to the bypassing agents and optimal laboratory tools.

Terminology

ITI: With ITI therapy, factor concentrate is given regularly over a period of time until the body is trained to recognize the treatment product without reacting to it.

Peer-review

The manuscript is written well.

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